Message

From: Kiely, Timothy [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=C4D74EAFD93C4FC7BC22DDBFFEA249D9-TIMOTHY M KIELY]
Sent: 6/15/2022 3:27:36 PM
To: Weissenborn, Lauren [Weissenborn.Lauren@epa.gov]; Bloom, Jill [Bloom.Jill@epa.gov]; Nguyen, Khue [Nguyen.Khue@epa.gov]
CC: Reaves, Elissa [Reaves.Elissa@epa.gov]; Britton, Cathryn [Britton.Cathryn@epa.gov]
Subject: RE: Difenoconazole

Thank you Lauren. I think this is all we need right now.

Tim

From: Weissenborn, Lauren <Weissenborn.Lauren@epa.gov>
Sent: Wednesday, June 15, 2022 11:19 AM
To: Kiely, Timothy <Kiely.Timothy@epa.gov>; Bloom, Jill <Bloom.Jill@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Reaves, Elissa <Reaves.Elissa@epa.gov>; Britton, Cathryn <Britton.Cathryn@epa.gov>
Subject: RE: Difenoconazole

Hi Tim:

Attached is the ID and the CFS comment as well as the comment attachments. Is this what you're looking for? Let me know if you're in need of anything else.

Thanks,
Lauren Weissenborn
Chemical Review Manager | RMIBV
Pesticide Re-Evaluation Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Weissenborn.lauren@epa.gov

From: Kiely, Timothy <Kiely.Timothy@epa.gov>
Sent: Wednesday, June 15, 2022 11:11 AM
To: Weissenborn, Lauren <Weissenborn.Lauren@epa.gov>; Bloom, Jill <Bloom.Jill@epa.gov>; Nguyen, Khue <Nguyen.Khue@epa.gov>
Cc: Reaves, Elissa <Reaves.Elissa@epa.gov>; Britton, Cathryn <Britton.Cathryn@epa.gov>
Subject: FW: Difenoconazole
Importance: High

Lauren,

Hello. Can you send us the final ID and the CFS comment? I pulled the following comment/response from the ID. I also pasted in the summary from program review that Jonah is referring to. Thank you.

Tim

From ID
Comments Submitted by the Center for Food Safety (Docket ID: EPA-HQ-OPP-2015-0401-0053 to 0057)
Comments pertaining to the ecological risk assessment:
Center for Food Safety (CFS) submitted several comments related to environmental fate and ecological effects outlined in the Agency's ecological risk assessment. CFS mentioned that difenoconazole is extremely persistent in laboratory and

field tests and is found in both water and soil. There is concern that EPA's exposure and risk assessments do not account for the accumulation of difenoconazole over a single season, or years.
CFS noted concern that the presented risks to terrestrial organisms do not capture the potential effect of difenoconazole on different taxa, specifically related to risk quotient (RQ) exceedances and difenoconazole's propensity to persist in the environment. It was stated that there are likely effects on ground-dwelling bees which was not adequately described in the Agency's risk assessment.
CFS stated that given the persistence of difenoconazole in terrestrial and aquatic environments repeated use can increase risks to aquatic organisms and increase the risks over time. CFS commented that difenoconazole can lead to bioaccumulation in fish and other aquatic organisms.
EPA Response: EPA considered the comment related to the persistence of difenoconazole in soil and water. The exposure modeling of aquatic environments is based on a collection of environmental fate properties as well as site-related input parameters. Additionally, variations in meteorological measurements were used to probabilistically estimate concentrations of difenoconazole in aquatic environments. These three things accounted for the accumulation of difenoconazole over a year and over multiple years.
The Agency's assessments rely on a surrogate species approach where a few tested species are used to represent sensitivity for all species. It is assumed that if honey bee data suggest level of concern (LOC) exceedances, then there is a risk concern for other bees, including ground-dwelling bees. When additional data are available for other terrestrial invertebrates, such as non-*Apis* bees, earthworms, and other soil dwelling invertebrates, that information is included in risk assessment as an additional line of evidence. For difenoconazole, no soil dwelling terrestrial invertebrate toxicity data are available, so refinement is not possible.
EPA acknowledges the risk for aquatic organisms and identified LOC exceedances for fish and aquatic invertebrates and disagrees with the comment that the Agency is not considering accumulation of difenoconazole over a year, or over multiple years. See the *Difenoconazole: EFED Response to Comments on the Proposed Interim Registration Review Decision (PID)* for more information.
Comments pertaining to the human health risk assessment:
CFS also submitted several comments related to the human health risk conclusions outlined in the Agency's human health risk assessment.
In 1994, the chronic reference dose EPA used was 0.01 mg/kg/day based on hepatocellular hypertrophy in male rats (MRID 42090019). In 2015, the chronic reference dose was retained, but the endpoint was changed to cumulative decreases in body weight gains. In the most recent 2020 human health risk assessment, the chronic reference dose was increased five-fold to 0.05 mg/kg/day and was based on a mouse instead of a rat study (MRID 42090015). CFS stated that EPA dismissed hepatocellular hypertrophy in male rats and that the current chronic reference dose value used for human health risk assessment is incorrect and should be reversed.
CFS noted that EPA originally classified difenoconazole as a Group C "Possible Human Carcinogen" in 1994, based on inducement of hepatocellular adenomas and carcinomas in a mouse study. In the 2020 human health risk assessment, EPA re-classified difenoconazole under the descriptor "Suggestive Evidence of Carcinogenicity." CFS suggested that the cancer classification should be reversed.
CFS asserted that a major metabolite of difenoconazole has been identified (CGA-205375) as present in humans, fish, and livestock. No toxicity data exists for the metabolite and CFS requested that EPA require that toxicity data be submitted.
Additionally, CFS asked EPA to require full dermal absorption data for various difenoconazole formulations and requested that the Agency conduct exposure assessments that incorporate a dermal absorption factor of 48% based on an older risk assessments, rather than the 6% dermal absorption factor derived from the dermal triple-pack approach.
CFS stated that triazole fungicides meet the criteria for designation as a common mechanism group and should have a cumulative assessment completed. CFS asserted that there are two endpoints, shared by most triazoles, that should be the focus of a cumulative risk assessment: fatty changes and carcinogenicity.
EPA Response: CFS correctly stated that the 2020 difenoconazole draft human health risk assessment used the no-observed adverse-effect level (NOAEL) from the mouse carcinogenicity study (4.7 mg/kg/day, from MRID 42090015) to derive a chronic population-adjusted dose (cPAD). That NOAEL is based on increased incidence of liver lesions (individual cell necrosis and bile stasis in males, hepatocyte hypertrophy in both sexes), and increased serum levels of serum sorbitol dehydrogenase (SDH) in males at a lowest-observed adverse-effect level (LOAEL) of 46 mg/kg/day. Older risk assessments used a NOAEL from a combined rat chronic toxicity/carcinogenicity study (0.96 mg/kg/day, from MRID 42090019) to derive the cPAD, based on cumulative decreases in body weight gains. However, the difenoconazole

toxicology database underwent extensive review for registration review in late 2020, and most studies were updated to reflect current toxicology evaluation practices. Changes in study LOAELs at that time prompted changes to the points of departure (PODs) selected for risk assessment. During the 2020 review, it was established that the rat combined chronic toxicity/carcinogenicity study determined the lowest-observed effect level (LOEL), not the lowest-observed adverse-effect level (LOAEL). Current Agency policy is to use only adverse effects, which are indicated by a LOAEL, not a LOEL, as a basis for risk assessment. The mouse study had a lower LOAEL than the rat study and was, therefore, selected to derive the cPAD.

EPA originally classified difenoconazole as a Group C Possible Human Carcinogen in 1994, based on clear inducement of hepatocellular adenomas and carcinomas in a mouse study. In 2007, in accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment*,[1] the Agency subsequently re-classified it under the descriptor Suggestive Evidence of Carcinogenicity based on liver tumors in male and female mice. This classification is consistent with current Agency guidelines. The reference dose would address the concern for chronic toxicity, including carcinogenicity, likely to result in exposure to difenoconazole.

EPA has reviewed the data that indicated a major metabolite of difenoconazole that has been identified (CGA-205375) as a residue of concern in humans, fish, and livestock. EPA uses structure-activity-relationship (SAR) analyses, as appropriate, to support decisions on residues of concern in situations where empirical data are lacking, and/or, to trigger the need for additional toxicology studies. In the case of difenoconazole, the SAR analysis of the metabolites using DEREK v.12 did not indicate any concerns for toxic effects that were not observed in the available difenoconazole toxicity database.

A dermal penetration study is conditionally required in the Code of Federal Regulations (CFR) Title 40 – Part §158.500, however, EPA has the flexibility to establish or modify data needs for individual pesticides and may require submission of additional data beyond what is specified. The dermal penetration study (guideline 870.7600) must be followed for *in vivo* studies in rodents, but it does not preclude use of other kinds of studies to derive a dermal absorption factor (DAF), such as *in vitro* skin absorption studies, or studies from the public scientific literature, or studies conducted under special protocols. Use of the triple pack approach is supported by EPA to refine dermal penetration results by accounting for differences between *in vitro* and *in vivo* absorption within a test species as well as species differences between animal and human skin. For registration review, the Agency used a DAF of 6% for human health risk assessment. The highest *in vivo* rat absorption from the available *in vivo* rat study was multiplied by the highest ratio of human vs. rat absorption from the available *in vitro* studies using technical difenoconazole.

The resulting DAF was considered a conservative estimate of absorption by human skin for difenoconazole at the time it was derived; however, the triple pack should be applied when similar protocols are utilized across the *in vitro* and *in vivo* studies, including the same test substance and similar dosing. Therefore, the DAF for difenoconazole has been reevaluated and based on all the available data and current practices, EPA has concluded that a DAF of 8% should be applied for difenoconazole moving forward. The updated DAF of 8% is similar to the previous DAF of 6% that was applied in the 2020 human health risk assessment and, therefore, this change does not materially impact the human health risk assessment.

The triazole fungicides share the following common metabolites: 1,2,4-Triazole (1,2,4-T), triazole alanine (TA), and triazole acetic acid (TAA). In 2006, the Agency issued aggregate human health risk assessments for 1,2,4-T and the conjugated metabolites of 1,2,4-T, TA and TAA. The assessment was based on sufficient data to support a risk assessment for these metabolites. The Agency conducted two assessments: one for 1,2,4-T and one for combined exposure to TA and TAA. Both assessments are highly conservative, using the maximum combination of uncertainty factors and high-end estimates of both dietary and non-dietary exposures. In addition, the 2006 aggregate assessments retained a 10X database uncertainty factor to account for the data gaps associated with the toxicological database and were designed to be extremely conservative so that the assumptions will remain valid for anticipated registrations. The Agency has not received any new data following the 2006 assessments, however; several requests for new uses of triazole fungicides have been submitted to the Agency and have been evaluated with the same conservatisms that were in place for the 2006 aggregate risk assessments. EPA does not believe that exposure or risk has been underestimated through these risk assessment approaches. The Agency will continue to employ a protective screening approach for all actions involving the triazoles and will continue to evaluate the need for additional data.

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[1] https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

The Agency has not assumed that difenoconazole has a common mechanism of toxicity with other substances at this time. The Agency will use the *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis*[2] to determine if the available toxicological data for difenoconazole suggest that a candidate common mechanism group may be established with other pesticides. If a common mechanism group is established, a screening-level analysis may be conducted to provide an initial screen for multiple pesticide exposure.
See the *Difenoconazole. Response to Comments on the Proposed Interim Decision* for more information.

Comments pertaining to fungicide resistance:

CFS noted that the triazole fungicides are the dominant compounds used to treat crops, animals, and humans and are the only class used in both medicine and agriculture. Triazoles used in human medicine include compounds such as itraconazole, voriconazole, and posoconazole. CFS noted concern regarding the development of resistance because the drivers of resistance in plant and human pathogens share some similarities. CFS expresses concern that the widespread use of triazole fungicides in agriculture may contribute to the development of fungal resistance to medical-use triazole drugs. CFS requested that the Agency assess the public health threats posed by continued and expanding use of difenoconazole and other agricultural triazoles in terms of increasing resistance of human fungal pathogens such as *A. fumigatus* and *C. auris* to medical antifungal compounds.

EPA Response: EPA is aware of increases in the total agricultural usage of both difenoconazole between 2015-2019 and triazoles more generally. EPA is also aware of increased global incidence of triazole-resistant human fungal pathogens. The extent to which the continued use of triazole fungicides to control plant pathogens in agricultural production may contribute to the emergence of antifungal resistant human pathogens is unclear and a direct association between the quantity of U.S. agricultural triazole fungicide use and human fungal infections has not been established.[3] EPA is working with federal partners to assess the potential impact of increased plant agriculture fungicide (e.g., difenoconazole) use in the U.S. on the development of triazole-resistance in medical settings. The Agency considers it critical that a variety of mode of action (MOA) groups remain available for use in the interest of suppressing resistance development to both agricultural and public health pathogens. For more information, see Section IV of this document and PRN 2017-1 and PRN 2017-2, available at https://www.epa.gov/pesticide-registration/pesticide-registration-notices-year.

From program review

Difenoconazole ID Summary

Release Interim Decision. Difenoconazole is a systemic broad-spectrum triazole fungicide registered for use as seed treatment on a number of cereal grain crops, cotton, canola, and potato seed pieces; as a foliar application to rice, fruits and nuts, vegetables, and field crops; and for post-harvest applications on some fruits and vegetables. Products containing difenoconazole are also registered for use on golf course turf and ornamental plants in commercial and residential landscaped areas. Difenoconazole is a demethylation inhibitor fungicide which acts by preventing development of fungal cell membranes in target pathogens giving it protective, curative, and eradicative properties against plant diseases. There are no human health risks of concern. There are potential ecological risks of concern for fish, aquatic invertebrates, birds, and mammals. Risks are considered low for honeybees and aquatic plants. Risk mitigation includes a requirement that treated seeds be soil-incorporated to limit exposure to birds and mammals. Label clarifications include restrictions for foliar rice uses in flooded fields, clarification of maximum annual application rates, advisory spray drift measures, surface and ground water advisories, a nontarget organism advisory, fungicide resistance management language, and updated glove language. Little to no impacts are expected from the risk mitigation. Public comments did not result in changes to the risk mitigation. *Anticipated stakeholder reaction*: Minimal stakeholder feedback is anticipated.

From: Richmond, Jonah <Richmond.Jonah@epa.gov>
Sent: Wednesday, June 15, 2022 10:34 AM
To: Reaves, Elissa <Reaves.Elissa@epa.gov>; Kiely, Timothy <Kiely.Timothy@epa.gov>
Cc: Keigwin, Richard <Keigwin.Richard@epa.gov>; Dinkins, Darlene <Dinkins.Darlene@epa.gov>

[2] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
[3] https://www.cdc.gov/fungal/diseases/aspergillosis/antifungal-resistant.htm

Subject: Difenoconazole
Importance: High

Elissa/Tim,

Do you have some more background on Difenoconazole? We have the press release from CFS's lawsuit (https://www.centerforfoodsafety.org/press-releases/6655/lawsuit-challenges-fungicide-that-causes-neurological-harms-and-imperils-wildlife-endangered-species) and the registration review summary (attached), but more background would be helpful, including about concerns we think CFS has, or concerns EPA has on it.

I'm copying Rick in case he has some additional guidance on what would be helpful.

Thanks,
Jonah

Jonah Richmond (He/Him/His)
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